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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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FENWICK & WEST LLP
SILICON VALLEY CENTER
801 CALIFORNIA STREET
MOUNTAIN VIEW, CA 94041

EXAMINER	
CHEN, SHIN LIN	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 10/06/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/086,118	HERRON, G. SCOTT	
	Examiner	Art Unit	
	Shin-Lin Chen	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 August 2004 and 17 September 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-8 and 12-46* is/are pending in the application.

4a) Of the above claim(s) *17-25,27,33,35 and 37-46* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 3-8, 12-16, 26, 28-32, 34 and 36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Upon further consideration of the subject matter of the claimed invention, the finality of the Official action mailed 6-25-04 has been withdrawn.

Applicants' amendment filed 8-2-04 has been entered. Claims 28 and 34 have been amended. Claims 1, 3-8 and 12-46 are pending. Claims 1, 3-8, 12-16, 26, 28-32, 34 and 36 are under consideration.

It should be noted that claim 26 is under consideration but not withdrawn as indicated in the amendment filed 8-2-04.

Inventorship

1. In view of the papers filed 9-17-04, it has been found that this nonprovisional application, as filed, through error and without deceptive intent, improperly set forth the inventorship, and accordingly, this application has been corrected in compliance with 37 CFR 1.48(a). The inventorship of this application has been changed by adding Jiwei Yang as coinventor.

The application will be forwarded to the Office of Initial Patent Examination (OIPE) for issuance of a corrected filing receipt, and correction of Office records to reflect the inventorship as corrected.

The oath/declaration filed 9-17-04 has been entered.

Priority

The amendment, filed 8-2-04, regarding paragraph [0001] on page 1 of the specification is improper. The phrase "; this application also is a continuation-in-part of and claims priority to

a United States patent application titled...converted from United States Provisional Application Serial No. 60/271,778, filed February 27, 2001" from line 9 to line 13 is redundant of the sentence from line 1 to line 5 of the same paragraph [0001]. Deletion of such redundancy is required.

Double Patenting

2. Applicant is advised that should claim 7 be found allowable, claim 30 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Claim Rejections - 35 USC § 101

1. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 34 and 36 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. A composition comprising isolated immortal human microvascular cells, wherein said cells form neovasculature and hot blood is transmitted through said neovasculature, includes a human body which has isolated immortalized microvascular cells grafted into said human body. Thus, the claim encompasses human beings which are not considered patentable subject matter. See MPEP 2105.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 1, 3-8, 12-16, 26, 28-32, 34 and 36 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a composition of endothelial cells comprising immortal human microvascular endothelial cells comprising a recombinant expression cassette encoding the disclosed full-length human telomerase, does not reasonably provide enablement for a composition of endothelial cells comprising immortal human microvascular endothelial cells comprising a recombinant expression cassette encoding any human telomerase other than the full-length human telomerase as disclosed, wherein said cells have a normal karyotype, are resistant to apoptosis relative to primary microvascular endothelial cells, and are not transformed, and a method of preparing said composition by introducing a recombinant vector into human endothelial cells in vivo via various administration routes. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Claims 1, 3-8, 12-16, 26 and 28-32 are directed to a composition of endothelial cells comprising immortal human microvascular endothelial cells comprising a recombinant expression cassette encoding a human telomerase, such as a human telomerase reverse transcriptase catalytic subunit, wherein said cells have a normal karyotype, are resistant to apoptosis relative to primary microvascular endothelial cells, and are not transformed, a method of producing said composition of endothelial cells, and the composition produced by said method

and the microvascular cells form neovasculature with host blood transmitted through said neovasculature. Claims 6 and 7 specify the cells stably express a genetic marker, such as enhanced green fluorescent protein (eGFP). Claims 8 and 12-16 specify the cells form human microvasculature in vitro and the growth of the human microvasculature is modulated by a compound that promotes angiogenesis, such as VEGF and FGF-2, or by a compound that is an anti-angiogenic compound, such as endostatin. Claim 30 specifies the immortal human microvascular endothelial cells further express eGFP. Claims 34 and 36 are directed to a composition comprising isolated immortal human microvascular cells that form neovasculature and the host blood is transmitted through said neovascualture. Claim 36 specifies said cells further express a genetic marker.

The claims encompass preparation of immortal human microvascular endothelial cells comprising a recombinant expression cassette encoding any human telomerase, including human telomerase variants other than the full-length human telomerase, in vitro or in vivo, wherein said cells have a normal karyotype, are resistant to apoptosis relative to primary microvascular endothelial cells, and are not transformed. The specification discloses preparation of a retroviral vector expressing full-length hTERT and transduction of commercial endothelial cells with said vector to produce hTERT(+)HDMEC (TERT1) cell line, and transduction of primary neonatal endothelial cells to produce hTERT(+)HDMEC (TERT2 and TERT3) cell lines (e.g. p. 58, 61). The hTERT(+)HDMEC cell lines form angiogenic webs when exposed to 3D type I collagen or Matrigel (e.g. p. 61). The hTERT(+)HDMEC cell lines show normal diploid karyotype and do not form colonies in soft agar (e.g. p. 63). Both TERT-1 and TERT-3 cell lines show resistance to apoptotic induction relative to primary HDMEC (e.g. p. 62). The hTERT(+) HDMEC cells

can form human blood vessels in SCID mice when SCID mice are implanted with Matrigel mixtures containing hTERT(+)HDMEC cells (e.g. p. 73).

The specification fails to provide adequate guidance and evidence for whether transfection or transduction of human endothelial cells with a recombinant expression cassette encoding any human telomerase, such as human telomerase variants or human telomerase reverse transcriptase subunit, in vitro or in vivo would result in immortal human microvascular endothelial cells having a normal karyotype, are resistant to apoptosis relative to primary microvascular endothelial cells, and are not transformed.

Kilian et al., 1999 (WO 99/01560), teach that human telomerase has 1132 amino acid residues and contain four major domains: N-terminal, basic, reverse transcriptase, and C-terminal (e.g. p. 9). Kilian also teaches that variants of the human telomerase sequences, which may result from alternative RNA splicing, are obtained by amplification and some of the variants encode truncated proteins and others have different C-terminal sequences (e.g. p. 10). The specification fails to provide the structural feature(s) within the human telomerase polypeptide that contributes to normal karyotype of the endothelial cells, the resistance to apoptotic induction, and non-transforming characteristics of the endothelial cells. One skilled in the art at the time of the invention would not know which region of the human telomerase is essential for producing immortal human microvascualr endothelial cells as claimed.

Further, the amino acid sequences of the variants of the human telomerase or the reverse transcriptase subunit could differ dramatically from that of the full-length human telomerase polypeptide. It was well known in the art that the amino acid sequence of a protein determines its structural and functional properties, and predictability of which amino acids can be removed

from a protein's sequence and still result in similar activity is extremely complex, and well outside the realm of routine experimentation, because accurate predictions of a protein's structure from mere sequence data are limited. Rudinger, 1976 (Peptide Hormones, Edited by Parsons, University Park Press, Baltimore, p. 1-7), points out that "The significance of particular amino acids and sequences for different aspects of biological activity cannot be predicted *a priori* but must be determined from case to case by painstaking experimental study" (e.g. p. 6). Kaye et al., 1990 (Proc. Natl. Acad. Sci. USA, Vol. 87, pp. 6922-6926) teaches that "A single amino acid substitution results in a retinoblastoma protein defective in phosphorylation and oncoprotein binding" (e.g. Title).

Skolnick et al., 2000 (Trends in Biotech, Vol. 18, p. 34-39) states "Sequence-based methods for function prediction are inadequate because of the multifunctional nature of proteins. However, just knowing the structure of the protein is also insufficient for prediction of multiple functional sites. Structural descriptors for protein functional sites are crucial for unlocking the secrets in both the sequence and structural-genomics projects" (e.g. abstract). Skolnick further states that "Knowing a protein's structure does not necessarily tell you its function" and "Because proteins can have similar folds but different functions, determining the structure of a protein may or may not tell you something about its function" (e.g. p. 36, box 2). In view of the lack of structural information that contributes to the claimed characteristics of the immortal human microvascular endothelial cells and the unpredictable nature of protein function from mere amino acid sequence, one skilled in the art at the time of the invention would not know how to use a recombinant expression cassette encoding any human telomerase, including variants of human telomerase and reverse transcriptase subunit, to prepare the claimed composition of endothelial

cells comprising the immortal human microvascualr endothelial cells having the claimed characteristic.

In addition, claims 31 and 32 encompass producing a composition of endothelial cells comprising immortal human microvascular endothelial cells by introducing a recombinant cassette encoding any telomerase into human dermal microvascular endothelial cells in vivo via various administration routes, and the microvascular cells form neovasculature with host blood transmitted through said neovasculature. The specification only discloses that the hTERT(+) HDMEC cells can form human blood vessels in SCID mice when SCID mice are implanted with Matrigel mixtures containing hTERT(+)HDMEC cells (e.g. p. 73). The human endothelial cells were transduced ex vivo with a recombinant retroviral vector expressing full-length human telomerase and the transduced endothelial cells were implanted into the SCID mice. The specification fails to provide adequate guidance and evidence for how to introduce a recombinant expression cassette encoding telomerase into human endothelial cells via various administration routes in vivo so as to produce a composition of endothelial cells comprising immortal human microvascular endothelial cells with the claimed characteristics and said microvascular cells form neovasculature with host blood transmitted through said neovasculature in vivo. Eck et al., 1996 (Goodman & Gilman's The Pharmacological Basis of Therapeutics, McGraw-Hill, New York, p. 77-101) reports that the fate of the DNA vector itself (volume of distribution, rate of clearance into the tissues, etc.), the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, and the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount and stability of the protein

produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced are all important factors for determining the efficiency of gene transfer in vivo (e.g. bridging pages 81-82). Thus, it would be unpredictable at the time of the invention whether introduction of a recombinant expression cassette encoding telomerase into human endothelial cells via various administration routes in vivo would result in a composition of endothelial cells comprising immortal human microvascular endothelial cells with the claimed characteristics and said microvascular cells form neovasculature with host blood transmitted through said neovasculature in vivo.

For the reasons discussed above, it would have required undue experimentation for one skilled in the art at the time of the invention to practice over the full scope of the invention claimed. This is particularly true given the nature of the invention, the state of the prior art, the breadth of the claims, the amount of experimentation necessary, the working examples given and scarcity of guidance in the specification, and the unpredictable nature of the art.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (571) 272-0726. The examiner can normally be reached on Monday to Friday from 9:30 am to 6 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson can be reached on (571) 272-0804. The fax phone number for this group is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Shin-Lin Chen, Ph.D.

SHIN-LIN CHEN
PRIMARY EXAMINER